

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-120

CHEMISTRY REVIEW(S)

DEC 16 1999

DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-120

CHEM. REVIEW # 4

REVIEW DATE: 12/15/99

RECOMMEND ACTION: APPROVABLE

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	10/31/95	10/31/95	11/30/95
AMENDMENT[AC]	4/14/97	4/15/97	4/20/97
AMENDMENT[AC]	11/24/97	11/24/97	11/24/97
AMENDMENT[AC]	3/13/98	3/16/98	3/17/98
AMENDMENT[BC]*	2/09/96	2/12/96	8/11/99
AMENDMENT[AZ]*	7/22/99	7/22/99	8/11/99
AMENDMENT[BC]*	9/24/99	9/27/99	9/27/99
AMENDMENT[BC]*	10/14/99	10/15/99	10/15/99
AMENDMENT[BZ]*	10/14/99	10/18/99	10/18/99
AMENDMENT[BC]*	10/29/99	11/1/99	11/10/99
AMENDMENT[C]*	11/22/99	11/24/99	11/30/99

*Subject of this review

NAME & ADDRESS OF APPLICANT:

Muro Pharmaceuticals Inc.
890 East Street
Tewksbury, MA 01876-1496

DRUG PRODUCT NAME

Proprietary:

Nonproprietary/USAN:

Code Name/#:

Chem. Type/Ther. Class:

Tri-Nasal Spray
triamcinolone acetonide nasal spray, 50 mcg
CAS #76-25-5
3S

ANDA Suitability Petition/DESI/Patent Status:

Submitted under 505 (b)(2). Claims a
3-year market exclusivity.

PHARMACOL. CATEGORY/INDICATION:

glucocorticosteroid with anti-inflammatory
and anti-allergic properties for treatment of
seasonal and perennial allergic rhinitis

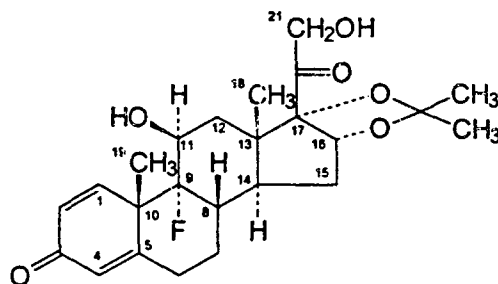
DOSAGE FORM:

Metered nasal pump spray (solution). 2 sprays per nostril.

STRENGTHS: Tri-Nasal Spray delivers _____ (based on submitted data) solution
containing 50 µg of triamcinolone acetonide per spray. The bottle is nominally _____ mL for a labeled
120 sprays.

ROUTE OF ADMINISTRATION:

Nasal Inhalation

DISPENSED: X Rx OTCCHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOLECULAR WEIGHT:

9-Fluoro-11 β ,16 α ,17,21-tetrahydroxypregna-1,4-
diene-3,20-dione cyclic 16,17-acetal with acetone
Molecular Formula: C₂₄H₃₁FO₆
Molecular Weight: 434.51

SUPPORTING DOCUMENTS:DMFs:

DMF No.	Holder Name	Subject	Status	Date Reviewed	Reference in CR
			Adequate	11/3/99	Chem Review #4
			Withdrawn		Page 7 of Chem. Review #3
			Withdrawn		Page 7 of Chem. Review #3
			Adequate	9/5/97	Item 4g of Chem. Review #2
			Adequate	9/5/97	Item 4g of Chem. Review #2
			Adequate	3/18/98	Item 20 of Chem Review #3
			Adequate	4/12/96	Not referenced in original submission or CR #1, referenced in CR #2
			Inadequate*	9/20/99	Response 12 of Chem Review #4

* The DMF was found inadequate and a deficiency letter was sent to the DMF holder on September 22, 1999. However, the NDA applicant addressed integrity issues in the amendment dated July 22, 1999.

<u>Type</u>	<u>Number</u>	<u>Owner</u>	<u>Subject</u>
NDA	19-798	Rhône-Poulenc Rorer	Nasacort® Nasal Inhaler (Approved)
IND	←	Muro Pharmaceuticals	triamcinolone acetonide nasal solution, 0.05%

CONSULT	DATE FORWARDED	STATUS	COMMENTS
EER	August 12, 1997 September 24, 1999	Acceptable Pending	CR #3, p. 4 FUR requested
Microbiology, HFD-160	August 6, 1996 Amendment forwarded June, 1997	Deficient 8/13/96 Adequate 8/5/97	See CR #2, item #20
Biometrics, HFD-710	Submitted on December 6, 1999	Complete	**
Environmental Assessment		Acceptable	See CR #3, p. 41
Pharmacology	Consult request for pump and extractables, level of impurity, and in the new formulation .	Complete	See attached Pharm/Tox Review dated 11/1/99
Methods Validation	Withheld until issues are resolved	To be submitted	
Labeling & Nomenclature Committee	February 1, 1996	NA 4/4/96 Acceptable*	See CR #1, p. 24

- * Review team overruled the LNC and accepted the proposed name (see PM's memo attached).
- ** Biometrics consult indicates that applicant's proposed expiration dating period should be reduced. I recommend 15 months at the time of approval.

CONCLUSIONS & RECOMMENDATIONS:

The application as submitted is approvable from the standpoint of chemistry, manufacturing, and controls provided that FUR for EER is satisfactory.

Note: The ^{approvable} approval letter should, also include any commitments made by the applicant. /S/

/S/

Chong Ho Kim, Ph.D.
Review Chemist

cc:

Org. NDA 20-120

HFD-570/Division File

HFD-570/CHKim

HFD-570/SBarnes

HFD-570/GPoochikian

HFD-570/RNicklas

R/D Init by: /S/ *KLP 12/16/99*

File name: n20-120r4d.fin

**APPEARS THIS WAY
ON ORIGINAL**

NDA 20-120

MAR 19 1998

DIVISION OF PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-120 **CHEM. REVIEW #** 3 **REVIEW DATE:** 3/19/98

Drug substance Brian Rogers, Ph.D.
Drug product Linda Ng, Ph.D.

RECOMMEND ACTION: NOT APPROVABLE

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	10/31/95	10/31/95	11/30/95
Amendment N AC	4/14/97	4/15/97	4/17/97

Subject of this review:

Amendment N AC	11/24/97	11/24/97	12/1/97
Amendment N AC	3/13/98	3/16/98	3/17/98

NAME & ADDRESS OF APPLICANT: Muro Pharmaceuticals Inc.
890 East Street
Tewksbury, MA 01876-1496

DRUG PRODUCT NAME

<u>Proprietary:</u>	Tri-Nasal Spray
<u>Nonproprietary/USAN:</u>	triamcinolone acetonide nasal solution, 0.05%
<u>Code Name/#:</u>	CAS #76-25-5
<u>Chem. Type/Ther. Class:</u>	3S

ANDA Suitability Petition/DESI/Patent Status: Submitted under 505 (b)(2). Claims a 3-year market exclusivity.

PHARMACOL. CATEGORY/INDICATION: glucocorticosteroid with anti-inflammatory and anti-allergic properties for treatment of seasonal and perennial allergic rhinitis

DOSAGE FORM: Metered nasal pump spray (solution). 2 sprays per nostril

STRENGTHS: Tri-nasal Spray delivers _____ (based on submitted data) solution containing 50 µg of triamcinolone acetonide per spray. The bottle is nominally _____ mL for a labeled 120 actuations.

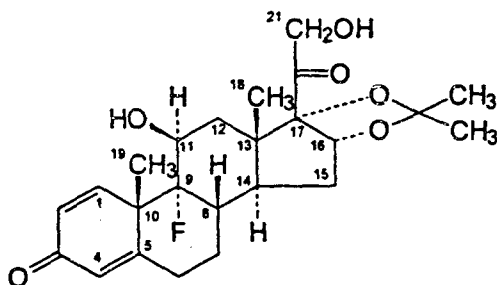
ROUTE OF ADMINISTRATION: Nasal Inhalation

NDA 20-120

DISPENSED:

X Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



9-Fluoro-11 β ,16 α ,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone

Molecular Formula: $C_{24}H_{31}FO_6$

Molecular Weight: 434.51

SUPPORTING DOCUMENTS:

DMFs:

DMF No.	Holder Name	Subject	Status	Date Reviewed	Reference in CR#1 review
			Inadequate	3/19/98	Item 20 of Chem review #3
			Withdrawn	3/19/98	Page 7 of Chem. Review #3
			Withdrawn	3/19/98	Page 7 of Chem. Review #3
			Adequate	9/5/97	Item 4g of Chem. Review #2
			Adequate	9/5/97	Item 4g of chem review #2
			Adequate	3/18/98	Item 20 of chem review #3
			Adequate	Adequate	Not referenced in original submission or CR #1, referenced in CR #2

RELATED DOCUMENTS (if applicable):

Type Number
NDA 19-798
IND

Owner
Rhône-Poulenc Rorer
Muro Pharmaceuticals

Subject
Nasacort® Nasal Inhaler (Approved)
triamcinolone acetonide nasal solution,
0.05%

CONSULTS:

CONSULT	DATE FORWARDED	STATUS	COMMENTS
EER	February 26, 1996 August 12, 1997	Acceptable	See CR #1, p. 14 See CR#3, p. 4
Microbiology, HFD-160	Evaluate from microbiological perspective, <u> </u> bulk and finished product release, in-vitro tests August 6, 1996 Amendment forwarded June 1997 with no consult form.	Deficient dated 8/13/96 Adequate 8/5/97	See CR #2, item #20
Biometrics, HFD-710	Withheld until pertinent stability issues are resolved		See CR #2, item 16
Environmental Assessment		Acceptable	See CR #3, p. 41
Methods Validation	Withheld until issues are resolved		
Labeling & Nomenclature Committee	February 1, 1996	NA 4/4/96	See CR #1, p. 24
Pharmacology	In vivo biological reactivity test, extractable for bottle and pump components. June 24, 1997	Acceptable 9/8/97	See CR #2, items 4e & 4f
Pharmacology	<u> </u> impurities in stability data. March 3, 1998	Open	

CONCLUSIONS & RECOMMENDATIONS:

The application as submitted is not approvable from the standpoint of chemistry, manufacturing, and controls. Deficiencies, detailed in the accompanying review notes and summarized in the attached list of deficiencies and comments along with any comment from pharmacologist (see consult), should be promptly forwarded to the applicant.

cc:

Org. NDA 20-120
HFD-570/Division File
HFD-570/BRogers
HFD-570/LNg
HFD-570/SBarnes
HFD-570/GPoochikian

R/D Init by: /S/ 3/19/98
Filename: 20120C.CMB

/S/
Brian D. Rogers, Ph.D. Review Chemist
(Drug substance)

/S/
Linda Ng, Ph.D. Review Chemist
(Drug product)

APPEARS THIS WAY
ON ORIGINAL

SEP 23 1997

/S/

NDA 20-120

DIVISION OF PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-120 **CHEM. REVIEW #** 2 **REVIEW DATE:** 9/19/97

Drug substance Brian Rogers, Ph.D.
Drug product Linda Ng, Ph.D.

RECOMMEND ACTION: NOT APPROVABLE

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	10/31/95	10/31/95	11/30/95

Subject of this review:
Amendment N AC 4/14/97 4/15/97 4/17/97

NAME & ADDRESS OF APPLICANT: Muro Pharmaceuticals Inc.
890 East Street
Tewksbury, MA 01876-1496

DRUG PRODUCT NAME

<u>Proprietary:</u>	Tri-Nasal Spray
<u>Nonproprietary/USAN:</u>	triamcinolone acetonide nasal solution, 0.05%
<u>Code Name/#:</u>	CAS #76-25-5
<u>Chem. Type/Ther. Class:</u>	3S

ANDA Suitability Petition/DESI/Patent Status: Submitted under 505 (b)(2). Claims a 3-year market exclusivity.

PHARMACOL. CATEGORY/INDICATION: glucocorticosteroid with anti-inflammatory and anti-allergic properties for treatment of seasonal and perennial allergic rhinitis

DOSAGE FORM: Metered nasal pump spray (solution). 2 sprays per nostril

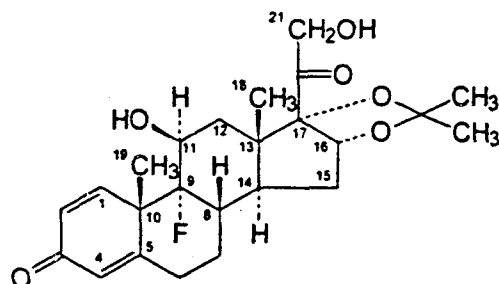
STRENGTHS: Tri-nasal Spray delivers (based on claim) solution containing 50 µg of triamcinolone acetonide per spray. The bottle is nominally — mL for a labeled 120 actuations.

ROUTE OF ADMINISTRATION: Nasal Inhalation

DISPENSED: X Rx OTC

NDA 20-120

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



9-Fluoro-11 β ,16 α ,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone

Molecular Formula: $C_{24}H_{31}FO_6$
Molecular Weight: 434.51

SUPPORTING DOCUMENTS:

DMFs:

DMF No.	Holder Name	Subject	Status	Date Reviewed	Reference In Chem Review
			Inadequate	9/4/97	Item 4g of Chem review #2
			Inadequate*	9/5/96	Page 6 of Chem. Review #1
			Inadequate	8/29/97	Page 6 of Chem. Review #1
			Adequate	4/12/96	Not referenced in original submission or CR #1
			Adequate		Item 4g of Chem. Review #2
			Adequate	9/5/97	Item 4g of chem review #2
			Inadequate	9/4/97	Item 4g of chem review #2

* Holder of _____ has subsequently withdrawn reference to _____
now is only DMF to be referenced for _____ All information pertaining to _____
must now be incorporated into _____

RELATED DOCUMENTS (if applicable):

Type	Number	Owner	Subject
NDA	19-798	Rhône-Poulenc Rorer	Nasacort® Nasal Inhaler (Approved)
IND	_____	Muro Pharmaceuticals	triamcinolone acetonide nasal solution, 0.05%

CONSULTS:

CONSULT	DATE FORWARDED	STATUS	COMMENTS
EER	February 26, 1996	Acceptable	See CR #1, p. 14
Microbiology, HFD-160	Evaluate from microbiological perspective, bulk and finished product release, in-vitro tests August 6, 1996 Amendment forwarded June 1997 with no consult form.	Deficient dated 8/13/96 Adequate 8/5/97	See CR #2, item #20
Biometrics, HFD-710	Withheld until pertinent stability issues are resolved (updated)		See CR #2, item 16
Environmental Assessment	Withheld until issue resolved; ask for request for categorical exclusion	Info request	See CR #2, item 22
Methods Validation	Withheld until issues are resolved		
Labeling & Nomenclature Committee	February 1, 1996	NA 4/4/96	See CR #1, p. 24
Pharmacology	In vivo biological reactivity test, extractable for bottle and pump components. June 24, 1997	Acceptable 9/8/97	See CR #2, items 4e & 4f

CONCLUSIONS & RECOMMENDATIONS:

The application as submitted is not approvable from the standpoint of chemistry, manufacturing, and controls. Deficiencies are detailed in the accompanying review notes and summarized in the attached list of deficiencies and comments. The deficiencies and comments should be promptly forwarded to the applicant. Labeling comments are deferred. Labeling comments are listed under item 23 a-g but not included in the deficiency letter.

cc:

Org. NDA 20-120

HFD-570/Division File

HFD-570/BRogers/9/10/96

HFD-570/LNg/9/10/96

HFD-570/SBarnes

HFD-570/GPoochikjan

R/D Init by: SL 9/23/97

Filename: 97-04-14.REV

/S/
 Brian D. Rogers, Ph.D. Review Chemist
 (Drug substance)

/S/
 Linda Ng, Ph.D. Review Chemist
 (Drug product)

**APPEARS THIS WAY
ON ORIGINAL**

DIVISION OF PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-120 **CHEM. REVIEW #** 1 **REVIEW DATE:** 9/10/96

Drug substance Brian Rogers, Ph.D.
Drug product Linda Ng, Ph.D.

RECOMMEND ACTION: NOT APPROVABLE

SUBMISSION TYPE **DOCUMENT DATE** **CDER DATE** **ASSIGNED DATE**

ORIGINAL 10/31/95 10/31/95 11/30/95

NAME & ADDRESS OF APPLICANT: Muro Pharmaceuticals Inc.
890 East Street
Tewksbury, MA 01876-1496

DRUG PRODUCT NAME

Proprietary: Tri-nasal Spray
Nonproprietary/USAN: triamcinolone acetonide nasal solution, 0.05%
Code Name/#: CAS #76-25-5
Chem. Type/Ther. Class: 3S

ANDA Suitability Petition/DESI/Patent Status: Submitted under 505 (b)(2). Claims a 3-year market exclusivity.

PHARMACOL. CATEGORY/INDICATION: glucocorticosteroid with anti-inflammatory and anti-allergic properties for treatment of seasonal and perennial allergic rhinitis

DOSAGE FORM: Metered nasal pump spray (solution). 2 sprays per nostril

STRENGTHS: After initial priming (number of priming actuations to be clarified), Tri-nasal Spray delivers 100 µL solution containing 50 µg of triamcinolone acetonide per spray from the nasal adapter. Delivery from the valve is also 50 µg of triamcinolone acetonide per actuation. The — valve is nominally a 100-µL metered-dose valve. The round amber PET — bottle is nominally — mL for a labeled 120 actuations. Target fill weights: — (120 actuations). Triamcinolone acetonide is optically active. Storage is labeled at —

ROUTE OF ADMINISTRATION: Nasal Inhalation

DISPENSED: X Rx OTC

CONSULTS:

CONSULT	DATE FORWARDED	STATUS	COMMENTS
EER	February 26, 1996	Acceptable	See CR #1, p. 14
Microbiology, HFD-160	August 6, 1996	Deficient 8/13/96	See CR #1, p. 21
Biometrics, HFD-710	Withheld until pertinent stability issues are resolved (updated)		
Environmental Assessment	Comment in pharmacology's and CR #1	Deficient	See CR #1, p. 24
Methods Validation	Withheld until issues are resolved	Deficient	
Labeling & Nomenclature Committee	February 1, 1996	NA 4/4/96	See CR #1, p. 24

CONCLUSIONS & RECOMMENDATIONS:

The application as submitted is not approvable from the standpoint of chemistry, manufacturing, and controls. Deficiencies are detailed in the accompanying review notes and summarized in the attached draft letter to the applicant, chemistry portion. These deficiencies should be promptly forwarded to the applicant. The name "Tri-Nasal" is considered not acceptable and has been brought to the attention of the review team.

cc:

Org. NDA 20-120

HFD-570/Division File

HFD-570/BRogers/9/10/96

HFD-570/LNg/9/6/96

HFD-570/SBarnes

HFD-570/GPoochikian

HFD-570/ASaavedra-Delgado

R/D Init by: LSI 9/11/96

filename: 20120.001

/S/
Brian D. Rogers, Ph.D. Review Chemist

/S/
Linda Ng, Ph.D. Review Chemist

APPEARS THIS WAY
ON ORIGINAL